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EVALUATION OF FLURAZEPAM AND PLACEBO  
ON SLEEP DISORDERS IN CHILDHOOD

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Benzodiazepines have largely been used in sleep disorders due to their anxiolytic and hypnotic action. Easy handling, few side effects<sup>43,60</sup>, and efficacy justify this preference. Although most studies in the literature concern insomnia in adults, those drugs have also been used in sleep disorders in children<sup>21</sup>. Among benzodiazepines, flurazepam is of great interest for its prolonged action, minimum side effects, low sedative action and minimum inducing effect over the hepatic microsomal enzymatic system; furthermore, it can act for longer periods, compared to other hypnotic drugs<sup>11,38</sup>. Although it is proved to be efficient in adults and also indicated for children<sup>46</sup>, there is a lack of controlled studies and with adequate statistical analysis in childhood. In the present study we tried to evaluate the middle term action of flurazepam in sleep disorders in infancy and childhood, compared with placebo.

MATERIAL AND METHODS

Forty patients of both sexes (22 boys and 18 girls) whose ages ranged between 1 and 15 years were selected. They had been referred to the out-patient department of Neuropediatrics for presenting one or more of the following sleep disorders: somnambulism, sleep terror and sleep-talking. As a criterion to be included in this group we consider that any of these disturbances should be occurring once or more than once a week and constitute the case's chief complaint. Patients who presented at the same time other sleep disorders, had these disorders analysed only when happening one or more times a week.

Out of the 40 patients, 5 (12.5%) had past histories of epilepsy: 4 of them using chronically phenobarbital (3 to 5 mg/kg/day) and 1 carbamazepine (20 mg/kg day)

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together with the drug studied. All of them had their seizures controlled for over one year.

The disorders presented were: sleepwalking, sleep-talking, sleep-related bruxism, sleep terror, excessive movements when sleeping, sleep-related headbanging and insomnia (Table 2). Two or more disturbances were observed in 32 (80%); three or more disturbances in 22 (55.0%) and in these, the most frequent triad was somnambulism, sleep-talking and excessive movements during sleep, observed in 12 cases.

Age in years	Number of cases
1 to 3	9
4 to 6	10
7 to 9	12
10 to 12	7
13 to 15	2
Total	40

Table 1 — Number and age of children with sleep disorders.

Sleep disorders	Number of cases
Excessive movements when sleeping	29 (72.5%)
Sleep-talking	26 (65.0%)
Sleepwalking	24 (60.0%)
Sleep-related bruxism	15 (37.5%)
Sleep terror	9 (22.5%)
Insomnia	3 ( 7.5%)
Sleep-related headbanging	2 ( 5.0%)

Table 2 — Sleep disorders in 40 patients aged 1 to 15 years.

Out of the total sampling, 35 (87.5%) were administered flurazepam and placebo isolately; the other 5 (12.5%) received them associated with the anticonvulsants. In all cases, flurazepam was the first and only drug with a hypnotic purpose. All parents and patients were informed that a test would be carried out with two different drugs and they gave their consent. All of them received initially placebo in the dose of half a tablet at bedtime for two weeks followed by flurazepam, also half a tablet at bedtime for two more weeks. Each tablet of placebo contained 200mg of ferrous sulfate. Each tablet of flurazepam contained 30mg of the drug. The interval between the clinical assessments was two weeks for all patients and they all underwent, at first, routine electroencephalogram (EEG) and complete blood count.

The evaluation of the results was carried out by using the following designation: no response (N) when the patients presented no improvement in the frequency of the sleep disorders or when there was a worsening of the symptoms; regular (R) when there was a decrease of 50% or less; good (G) when the reduction was between 51 and 75%; very good (VG) when between 76 and 100%. In the statistical calculations we considered initially as equal the difference intervals among the several degrees of improvement (VG,G,R,N) and we observed through the Signal test <sup>62</sup> the difference between the results with placebo and with flurazepam. This calculation was carried out for each disorder separately. Whenever the sample had less than 25 individuals, we compared the difference by the Binomial test <sup>62</sup> and when it had more than 25 we did it by Normal Distribution <sup>62</sup>. As a second approach, trying to observe better the relations of results we performed a comparison of the frequency of differences. In this comparison, whenever the expected frequency was greater or equal to 5 we used the test of  $\chi^2_1$  and when smaller than 5, the Binomial test.

Placebo	Flurazepam			
	N	R	G	VG
N			2	14
R				3
G				
VG				6

*Table 3 — Responses to the use of flurazepam and placebo in 24 cases of somnambulism. VG= reduction from 76 to 100%; G= reduction of 51 to 75%; R= reduction of 50% or less; N= no effect or worsening.*

## RESULTS

In 24 cases of sleepwalking, 18 had an improvement when passing from placebo to flurazepam (Table 3) which is highly significant ( $p < 0.001$ ). When we compared the number of patients who remained unaltered with the ones who improved, we noticed an important difference ( $0.02 > p > 0.001$ ). The difference between those who had a remarkable improvement when shifting from N with placebo to VG with the drug and the others was not significant.

We observed 26 cases of sleep-talking and noticed improvement in 23 when changing from placebo to the drug (Table 4), which is highly significant ( $p < 0.0001$ ). The difference between the number of children who improved and the ones without alterations was remarkable ( $p < 0.001$ ) It must be pointed out that 18 out of the 25 cases had a remarkable improvement passing from N with placebo to VG with the drug which is significant when compared with other 8 patients ( $0.05 > p > 0.02$ )

Placebo	Flurazepam			
	N	R	G	VG
N		1		18
R				3
G				1
VG				3

*Table 4 — Response to the use of flurazepam and placebo in 26 cases of sleep-talking. VG= reduction from 76 to 100%; G= reduction of 51 to 75%; R= reduction of 50% or less; N= no effect or worsening.*

Placebo	Flurazepam			
	N	R	G	VG
N	1	1	3	19
R				3
G				1
VG				1

*Table 5 — Response to the use of flurazepam and placebo in 29 cases with excessive movement when sleeping. VG= reduction from 76 to 100%; G= reduction of 51 to 75%; R= reduction of 50% or less; N= no effect or worsening.*

Among the 15 patients with bruxism, 9 presented improvement when passing from placebo to the hypnotic drug (Table 6), which is an important difference ( $p=0.002$ ). The comparison by  $\chi^2_1$  test between those who did not show alterations and all the ones who improved, as well as the comparison between those with little improvement and the ones in which the improvement was remarkable, was not significant.

Sleep terror was observed in 9 patients, 5 of which improved when changing to flurazepam ( $p=0.031$ ), which is an important result since none of them presented better results with placebo (Table 7). On the other hand, there was no difference between the number of children who remained unaltered (4) and the ones who improved (5) when passing from the placebo to the drug.

Excessive movement when sleeping was the most frequent complaint; it was reported in 29 patients out of which 27 improved when changed from placebo to flurazepam (Table 5), which is significant ( $p<0.00003$ ). It was significant the difference between the ones who had N or R with placebo and G or VG with the benzodiazepine, i.e., the ones who had a remarkable improvement in relation to the others ( $p<0.001$ ).

Placebo	Flurazepam			
	N	R	G	VG
N	1	1		7
R				1
G				
VG				5

*Table 6 — Response to the use of flurazepam and placebo in 15 cases of sleep-related bruxism. VG= reduction from 76 to 100%; G= reduction of 51 to 75%; R= reduction of 50% or less; N= no effect or worsening.*

Placebo	Flurazepam			
	N	R	G	VG
N	1			5
R				
G				
VG				3

*Table 7 — Response to the use of flurazepam and placebo in 9 cases of sleep terror. VG= reduction from 76 to 100%; G= reduction from 51 to 75%; R= reduction of 50% or less; N= no effect or worsening.*

Patients who presented sleep-related headbanging and insomnia were very few and do not represent a statistical analysis. In the two cases with sleep-related headbanging, one presented improvement with flurazepam and no improvement with placebo. The three cases with insomnia revealed results VG with flurazepam and N with placebo.

Side effects were reported by the parents in three cases with placebo and six cases with flurazepam (Table 8). The children who showed these effects with placebo were 2, 4 and 12 years old; the ones with the drug were 1, 2, 3, 5, 7 and 8 years old. Therefore, the age of the patients was not correlated. In the total of side effects, flurazepam had to be discontinued in 2 cases (3 and 8 years old). These patients presented mild vomiting and excessive drowsiness during the first three days which led us to reduce the dose for 7.5mg daily but, as this manifestation still persisted in the three following days, the drug was discontinued.

General clinical examination and neurologic tests were normal in all cases studied. The EEG performed in all patients before the test was normal in 35 (87.5%); in the

other 5 children, 3 (7.5%) presented left temporal irritative activity; 1 (2.5%) right mid-temporal irritative activity; 1(2.5%) midline fronto-parietal irritative activity. In these 5 patients with EEG alterations, only 2 had past histories of seizures and were taking anticonvulsants. In the 5 patients of the total sampling who had been taking anticonvulsants, only 2 had EEG alterations.

Complete blood count performed in all patients showed to be normal in 24 (60.0%) and in the others we observed mild anemia in 13 (32.5%) and only eosinophilia in 3 (7.5%). Among the patients with anemia, 3 had mild leukocytosis with a shift to the left and 3 had eosinophilia.

Side effects	Number of cases	
	Placebo	Flurazepam
Only drowsiness	1	1
Drowsiness, nausea and vomiting		2
Irritability	2	3

Table 8 — Side effects of flurazepam and placebo in 40 cases of sleep disorders in childhood.

#### COMMENTS

Flurazepam, i.e., 7-chloro-1-2-[-2-(diethylamino)ethyl]-5-0-fluorophenyl)-1,3-dihydro-2H-1,4 benzodiazepin-2-one is one of the most prescribed benzodiazepines in medical practice. After one only ingestion per os it reaches a serum peak in 1 hour and then falls suddenly with a 3 hour half life. Its main desaminated and desalkylated active metabolites which are even more powerful have a long half life of 10-20 hours and one day or more, respectively<sup>22</sup>. Therefore, its pharmacologic activity is attributed to its metabolites. As a hypnotic drug, it has the advantage of being efficient even when administered for a period of two weeks or more, i.e., longer than other drugs of this category<sup>33,34,36,38</sup>; it decreases the latency of sleep<sup>66</sup>; it decreases wake time during the night<sup>36</sup> and increases the total sleep time<sup>45</sup>. In polygraphic studies during the night it is observed that, like other benzodiazepines, it can decrease the activity of sleep spindles<sup>29</sup> and the number of K complex<sup>29</sup>. Stage 4 and less markedly 1 and 3 decrease with flurazepam just like other benzodiazepines in therapeutic doses<sup>6,14,23,33,34,36,37,39,45,67</sup>; it occurs concomitantly increase of time in stage 2<sup>14,39</sup> and minimum or no action over rapid eye movement (REM) stage<sup>29,33,45</sup>. Through a computerized it can be observed that despite the decrease of delta waves of stage 4, these waves increase in stage 2, compensating themselves and keeping a total constant of these waves<sup>44</sup>. The withdrawal of flurazepam does not cause a rebound effect of REM stage or of the other stages and this is another reason for its choice in relation to other hypnotic drugs<sup>22,25,33,36,37,39,48,67</sup>. A psychologic evaluation shows that even when administered for several days it does not have effect on the patient's

mood<sup>11</sup>; it does not affect short-term memory<sup>11</sup>; it provokes minimal psychomotor alterations on the following day<sup>10</sup> and, in adults, it induces a sleep which is subjectively more refreshing and restful<sup>7,11</sup>.

Sleepwalking is an automatism which presents during sleep, usually one to three hours after falling asleep. Its manifestations varies from sitting up in bed with stereotyped movements, up to walking around the room or even around the house in very complex activities. When waking up the patient does not remember the activity performed. Sleepwalking may occur in any age group but is more frequent in childhood and it seems to have a family influence. Polygraphic studies show that it occurs during stage 4. It starts with slow waves of high voltage which decrease progressively, characterizing an arousal reaction, usually just before the motor activation. As the stereotypes begin, a tracing of light sleep mixed with non-reactive alpha activity is noticed. Besides psychotherapy<sup>31</sup> and to protect the child against possible accidents<sup>35</sup>, drugs like benzodiazepines<sup>2,35,59</sup>, barbiturate<sup>31</sup>, meprobamate<sup>31</sup> and imipramine<sup>50</sup> have been used. We found in our study a significant decrease in the frequency of this disorder with flurazepam in relation to placebo. This result is of special interest because benzodiazepines are suppressors of stage 4 in which somnambulism and sleep terror take place. Therefore its use should be recommended in these disorders<sup>16,21,39</sup>, and flurazepam maintains this suppression even when used for a long time<sup>44</sup>; however, there are no evidences to substantiate it in the literature. Our observation in somnambulism and sleep terror are in accordance with this hypothesis.

Sleep terror is a dramatic episode in which the child who is sleeping calmly, suddenly performs violent movements, sometimes sitting up in bed with an expression of fear, shouting or crying, with tachycardia, tachypnea, profuse sweating and stereotyped movements. It occurs in the first half of the night and its duration is variable (between 1 and 20 minutes) and it can repeat several times in the same night<sup>40</sup>. On the following day the patient does not remember the event. On EEG, night terror is very similar to somnambulism and appears in stage 3 and 4<sup>15,28,65</sup> and, likewise can be interpreted as an abrupt liberation of autonomic activity, in conditions of an incomplete arousal. Besides the psychiatric approach, some drugs have been used like methylphenidate<sup>12</sup>, imipramine<sup>16,21,50</sup> and benzodiazepines<sup>4,16,17,20,21,35,41</sup> have been used with inconclusive results. We observed here a decrease in the frequency of the disorder in 5 cases with flurazepam while 4 remained unaltered and, no one improved with placebo. This difference between drug and placebo was statistically significant. It is interesting to notice that only half of the cases improved with flurazepam; however their improvement was always remarkable.

Sleep-talking is the speech during sleep, without a critical recognition of the event<sup>3</sup>. It takes place sporadically in childhood but the occurrence for one or more times a week, like in this study, has been seen in less than 20% of the population in this age group<sup>58</sup>. Sleep-talking may occur isolately or during episodes of somnambulism. EEG studies shows that it may occur in any stage<sup>52</sup>. We found a decrease of frequency of sleep-talking when passing

from placebo to flurazepam. This change occurred in several degrees but it is important to notice that 18 out of the 26 cases passed from effect N with placebo to VG with the drug, which is significant if compared to other responses.

Excessive movements during sleep is one of the most frequent sleep complaints of children who go to a neuropediatrician. In our study it was also the most frequent complaint (72.5% of the cases). It must be pointed out that when a child presents excessive movements during sleep, this fact does not limit one only disorder but, on the contrary, it is a characteristic that can accompany several disturbances being, sometimes, difficult to differentiate from normality. In our cases the response to the benzodiazepine was remarkable; 27 out of the 29 cases improved and 2 remained unaltered when shifting from placebo to the drug.

Other manifestations, besides the ones primarily investigated were also observed in those children, like sleep-related bruxism, sleep-related headbanging and insomnia, also in the frequency of one or more times a week. Bruxism is the forced contraction of some muscles of chewing leading to the noise of grinding of the teeth<sup>54</sup>. It may occur in any stage but especially during non-REMS and more frequently in stage 2 or transition between stages<sup>52,54,56,64</sup>. Children present this disorder more often than adults; there is no difference between sexes and it may be so intense up to the point of causing serious damage to the teeth<sup>5,64</sup>. Several etiologies have been proposed for this intriguing manifestation of sleep, from emotional tension<sup>24</sup> to bad occlusion of teeth, but without substantiation. Many times these episodes are accompanied by movements of the body and tachycardia. We found sleep-related bruxism in 37.5% of our patients and the difference between the improvement with benzodiazepine and with placebo was significant.

Sleep-related headbanging is the rhythmic swinging of the head which occurs just before falling asleep or during sleep<sup>61</sup>. Polygraphic studies show that it may occur in any stage but preferably in light sleep. It usually starts in infancy and has a self-limited course; however, in some cases it persists during adolescence or even adulthood. It is more frequent in children whose intelligence is below normal and when there are not organic factors, it seems to be associated to emotional tension. Many treatments have been proposed such as psychotherapy<sup>13</sup>, diazepam<sup>18</sup>, imipramine<sup>18</sup>, diphenylhydantoin<sup>18</sup> still with inconclusive results<sup>42</sup>. We found this alteration in only two cases and the response to flurazepam was G in one case and N in the other; the response to placebo was N in both cases. This limited sampling does not permit a statistical comparison.

Among all sleep disturbances, insomnia is the most studied at present, and the drugs of choice have been benzodiazepines. Flurazepam is one of the most used<sup>31</sup> in this group. All-night studies indicate that insomnia may have a great variety of quantitative and qualitative patterns, but the main forms are the difficulty to fall asleep, the frequent and prolonged arouse during the night,



and the early arousal. We observed only 3 cases of insomnia and they all had response VG to flurazepam and N to placebo. As this sampling is too small we were not able to perform a statistical comparison, but these data encourage its test in a larger sampling of insomniac children.

The normal finding both in the general clinical examination and neurologic test in all cases may be showing a tendency in the screening, since the patients with other manifestations usually are not referred to the authors for a study of sleep. Another reason is that the neurological test in its classic form is not the most adequate for evaluation of details in this age group and thus, perhaps the Neurological Evolutional Examination<sup>22</sup> might supply more information.

The finding of EEG alterations in only 5 cases (12.5%) and in these, 2 had past histories of seizures, is in accordance with the present concepts that these disturbances are not epileptic manifestations<sup>6</sup>. However, one must always have in mind that partial crises with complex symptomatology may occur occasionally during sleep<sup>19,28,31</sup>, thus simulating these alterations.

Complete blood counts were performed as control because we had been using ferrous sulfate as placebo, in spite of the small doses used. The findings of 32.5% of the cases with anemia and high percentage of eosinophilia, to our understanding, only reflects the low socio-economic conditions of the population examined by this department which is subject to poor feeding conditions and verminosis.

Side effects with flurazepam have been reported as minimum, usually mild drowsiness or dizziness during the day following the ingestion<sup>8,9,22</sup>. Side effects with placebos, although not frequent, may occur in patients with sleep disorders<sup>1,9</sup>. In our sampling we noticed that these effects were reported by the parents both with placebo and with the benzodiazepines, which indicates that the data should be analyzed cautiously. These data may be reflecting their fears towards the disorders or the therapy itself<sup>27</sup>. We observed one case of drowsiness by placebo and 3 by the drug. These figures are too small for statistical evaluation. Nauseas and vomiting were noticed in 2 cases with flurazepam and no one with placebo. There was no relationship between the side effect and age of the patient. In 2 cases drowsiness was severe enough to force the withdrawal of the benzodiazepine since there was no improvement with decrease of the dose, suggesting therefore that these 2 patients should have a greater individual susceptibility to the drug.

It must be said that we tried to observe only the isolated action of flurazepam in these disorders. However we consider that when analyzing these alterations it is sometimes necessary to have not just vision and neurologic therapeutics but also the emotional evaluation and psychotherapy<sup>32,40,57,59</sup>. It is important to remind that hypnotic drugs in general are indicated only for a restricted number of children and it is up to the physician to choose the cases carefully<sup>26,47,49,64</sup>.

## SUMMARY

The clinically observed results in 40 patients, from 1 to 15 years old, presenting sleep disturbances, in a comparative and statistically approached study of flurazepam 15mg daily against placebo, are reported. Placebo was administered, followed by the drug, during 14 days each. The chief complaints were sleepwalking, sleep-talking, sleep terror, sleep-related bruxism, sleep-related headbanging, insomnia and excessive movements during sleep. A significant effect of flurazepam on sleepwalking, sleep-talking, bruxism, sleep terror and excessive movement during sleep, was observed. The insomniac and headbanging patients were not enough for statistical analysis. Flurazepam side effects were excessive drowsiness during daytime in 3 cases; irritability, 3 cases; nausea and vomiting, 2 cases, and were not correlated with age. Placebo side effects were similar, except for nausea and vomiting which were not observed. It was necessary to discontinue flurazepam in 2 cases, because of excessive drowsiness during daytime, which did not improve when reducing the dose.

## RESUMO

*Avaliação de flurazepam e placebo nos distúrbios do sono na infância.*

Os autores relatam os efeitos de flurazepam e placebo em estudo comparativo, em 40 crianças com distúrbios do sono. As alterações observadas são: sonambulismo, terror noturno, sonilóquio, bruxismo durante o sono, jactatio capitis nocturnus, insonia e movimentação excessiva durante o sono. São analisadas a ação da droga assim como a ocorrência de efeitos colaterais.

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